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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/644,325	08/19/2003	Hans Weiher	VOS-44 CON	6657

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FISH & NEAVE IP GROUP
ROPES & GRAY LLP
1251 AVENUE OF THE AMERICAS FL C3
NEW YORK, NY 10020-1105

EXAMINER	
HARLE, JENNIFER I	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 07/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/644,325	WEIHER ET AL.	
	Examiner	Art Unit	
	Jennifer I. Harle	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *5-8 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-4 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/26/06*. 4
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00

DETAILED ACTION

1. Claims 1-10 were originally pending and subject to an Election/Restriction requirement. Group I, specific compound acivicin-125 and the species chronic renal diseases. Applicant via Response to Election/Restriction Requirement, filed April 4, 2005, withdrew claims 5-8 and 10.

Election/Restrictions

2. Applicant's election with traverse of Group I (claims 1-4 and 8-10) as it pertains the specific compound acivicin-125 and the species chronic renal disease, focal glomerulosclerosis, in the reply filed on April 4, 2005 is acknowledged. The traversal is on the ground(s) that restriction to a single inhibitors elecimnates Applicants' ability to obtain a generic claim to a method of treating by inhibiting the gamma-GT gene and that eliminating the derivatives of acivicin-125 is improper because examination of the derivatives would not constitute and undue search burden.. This is not found persuasive because the examination of all of the compounds as previously set forth would constitute an undue search burden because the compounds are not required to have any core structure and can vary greatly within each of the groups themselves and each of the different compound groups may have a separate status in the art via their potential to have separate classifications, may require structure searches, in cases where descriptive information is required non-patent technical databases will need to be search and cross referenced, chemical compounds may not be concomitant with peptide, etc., this was not refuted by Applicants nor was any core structure provided. Applicants argued that searching the derivatives would not constitute an undue search burden, however, as the examiner pointed out in the Election/Restriction, there was no definition of what the derivative encompassed – it is an isoxazoleacetic acid (nitrogen and oxygen ring containing compound) and its derivatives (resulting in an unlimited number of

compounds as derivatives allow for substitutions, deletions and additions in any place in the compound – including the ring –and thus would potentially result in a lack of a known core). Applicants did not refute this statement but merely said it would not constitute an undue burden nor did they provide any references, which would provide the examiner with guidance on the scope of the derivatives or a core for the derivatives sought. Thus, the derivatives are deemed to encompass all possible substitutions with no known core and result in thousands and thousands of compositions resulting in an undue burdensome search.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 5-8 and 10 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on April 4, 2005.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim1-4 and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that

> "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, no that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that

the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

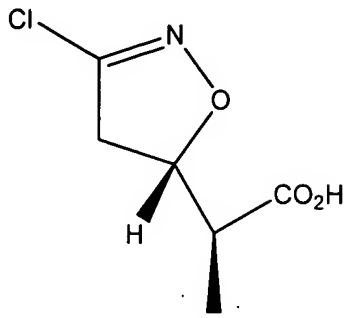
The factors considered in the Written Description requirement are (1) *level of skill and knowledge in the art*, (2) *partial structure*, (3) *physical and/or chemical properties*, (4) *functional characteristics alone or coupled with a known or disclosed correlation between structure and function*, and the (5) *method of making the claimed invention.*

In the instant case, the claims are drawn to treating degenerative diseases by inhibiting gamma-GT activity and using the inhibitor acivicin-125 and its derivatives to inhibit gamma-GT activity

(1) Level of skill and knowledge in the art:

The level of skill in the art is high. Treating all degenerative diseases by inhibiting an enzyme activity that is not well known requires knowledge of a plethora of field that would not necessarily overlap. Degenerative diseases range from joint diseases to neurological diseases to hereditary diseases, etc. and would require a thorough understanding of those field, as well as the enzyme pathway and various modeling. The knowledge in the art regarding the compound acivicin-125 is fairly well developed, however, as Applicants, have failed to place any restrictions on derivative, the compounds of the derivative can be quite complex and the level of skill in the art could range from simple chemistry, i.e. replacement of a hydrogen group, to complex replacements involving creating a peptide or protein out of this chemical structure as it itself is a derivative of glutamine.

(2) Partial structure:



Applicants did not define what was meant by derivatives anywhere in the Specification. Thus, the result is a plethora of compounds as derivative allow for substitution, deletions and additions in any place in the compound and would result in no known core. Additionally, they are treating any degenerative disease that is inhibited by gamma-GT activity. The number of degenerative diseases is incredibly long. See for example the printout of just the Medline listing of possible degenerative diseases used as MeSH terms, STN, June 27, 2005, pp. 1-14.

(3) Physical and/or chemical properties:

Acivicin-125 is a known anti-biotic that is a gamma-GT inhibitor. See, Cutrin, et al., Contribution of Gamma glutamyl transpeptidase to oxidative damage of ischemic rat kidney, Kidney International, February 2000, Vol. 57,pp. 526-533, esp. 531. As for the derivatives, the salts would be expected to function much like other salts. The enzyme pathways involved in all the degenerative diseases are still under investigation. Applicants have not provided any description for determining whether any given degenerative disease is inhibited by gamma-GT.

(4) Functional characteristics:

Acivicin-125 is a known anti-biotic that is a gamma-GT inhibitor. See, Cutrin, et al., Contribution of Gamma glutamyl transpeptidase to oxidative damage of ischemic rat kidney, Kidney International, February 2000, Vol. 57,pp. 526-533, esp. 531. Depending upon the degenerative disease, they can be idiopathic or mediated by numerous different pathways.

(5) Method of making the claimed invention:

Acivicin-125 can be made by routine chemical synthesis and is available for sale, as for the derivatives, as there is no common core, and Applicants' provide no written description of how to make any of the derivatives or determine their activity, except with respect to the accepted model for focal segmental glomerulal sclerosis and minimal change nephrosis, one can only suppose that some of the derivatives would be made by routine chemical synthesis, peptide synthesis, etc..

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim 1 is a broad generic, with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of acivicin derivatives. It must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the compound, it is not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed compound... MPEP § 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between only one function, inhibiting gamma-GT to treat focal segmental glomerulosclerosis/minimal change nephrosis and structure of the compounds beyond compound disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of any species of the derivatives to reflect this variance in the genus since the specification does not provide any examples of derivatives, or how to determine a core structure or how to screen them for the gamma-GT inhibitory activity or how to screen degenerative diseases for the gamma-GT function. While having written description of acivicin-125 as it pertains to inhibiting gamma-

GT for treating focal segmental glomerulosclerosis/minimal change and compounds identified in the specification tables and/or examples, the specification is void of any peptides, organic molecules that qualify for the functional characteristics claimed as the derivatives of acivicin-125 with functional characteristics that qualify.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: administering the an inhibitor/compound to the subject because without administering a compound there is no way to treat the degenerative disease unless the body inherently inhibits gamma-GT activity on its own.

8. Claim 9 recites the limitation ""said gamma-GT inhibitor" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-4 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cutrin, *et al.,* Contribution of Gamma glutamyl transpeptidase to oxidative damage of ischemic rat kidney, Kidney International, February 2000, Vol. 57, pp. 526-533 in view of Drozdz, et al., gamma Glutamyltransferase Dependent Generation of Reaction Oxygen Species from a Glutatione/Trasferrin System, Free Radical Biology & Medicine, 1998, Vol. 25, No. 7, pp. 786-792 and further in view of Binder, et al., Glomerular Over Production of Oxygen Radicals in Mpv17 Gene-Inactivated Mice Causes Podocyte Food Process Flattening and Proteinuria, American Journal of Pathology, April 1999, Vol. 154, No. 4, pp. 1067-1075.

Cutrin discloses that gamma-GT is a glycoprotein attached to the external cell surface of various cell types and in the kidney the primary site of gamma-GT activity is the outer surface of the microvillus membrane in the PT. Cutrin further discloses that because gamma-GT favors the reconstitution of intracellular GSH, it should be consider as a member of the anti-oxidant defense (ROS), using a rat model of unilateral renal ischemia the degree of tubular cell damage and lipid peroxidation was evaluated, the activity of gamma-GT in vivo was inhibit by pre-treating the animal with acivicin, a glutamine analogue that irreversable inactivate gamma-GT without affecting its synthesis and degradation. Cutrin also disclosed that acivin treated rats had ischemic kidneys that showed only mild cytological and architectural alteration of PT, as well as a slight histochemical positive reaction of gamma-GT activity. Thus, according to Cutrin, animal

pretreatment with a single dose of acivicin the most reliable gamma-GT inhibitor, able to prevent fully the effect of ischemia on the enzyme activity allowed protection of the ischemic organ against lipid peroxidation enhancement and morphological alterations, which indicate that the up-regulation of gamma-GT activity contributes to the ischemic damage of proximual tobular cells through a pro-oxidant effect and that the relatively late cleavage of the transpeptidase precursor in the posttranslational processing of the enzyme may therefore serve to prevent degradation of GSH in the cytoplasm. Thus, Cutrin discloses that acivicin is a potent gamma-GT inhibitor, which can be used to treat ROS mediated kidney diseases, where proximal tubular cells are damaged . However, Cutrin does not disclose that acivicin could be used to treat a chonic renal disease, such as focal segmental glomerulsclerosis or minimal change nephrosis. Drozdz discloses that gamma-GT generates ROS and that transfected V79 cells expressing human gamma-GT generated ROS, i.e. under physiological conditions, gamma-GT is directly involved in ROS generation – gamma-Gt is an ubiquitous enzyme involved in cellular metabolism of GSH, which catalyzed transfer of gamma-glutamyl moiety from GSH to amino group acceptors such as amino acids of peptds and has paradoxically been connected with oxidative damage. Pp. 786, 790-791. Binder discloses that focal segmental glomerulsclerosis or minimal change nephrosis are relatively frequent glomerular diseases and that in these and there is a direct correlation between focal segmental glomerulsclerosis or minimal change nephrosis and their murine test and several other glomerular diseases and overproduction of reactive oxygen species (ROS) and local accumulation of lipid peroxidation (LPO) adducts were identified as pre causes for glomular damage, which is a murine model for testing compounds for treatment. Pg. 1067, 1073-1074. Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention to have used acivicin to treat

focal segmental glomerulsclerosis or minimal change nephrosis, as it was known that gamma-GT can generate ROS, acivicin is a potent inhibitor of gamma-GT, acivicin can already be used to treat renal problems due to the up-regulation of gamma-GT activity and prevents damage to proximal tubular cells, ROS is instrumental in focal segmental glomerulsclerosis or minimal change nephrosis. Moreover, there is a ready model for screening.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer I. Harle whose telephone number is (571) 272-2763. The examiner can normally be reached on Monday through Thursday, 6:30 am to 5:00 pm,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jennifer I. Harle
Examiner
Art Unit 1654

June 27, 2005